REMARKS

I. Status Summary

Claims 1-35 were filed with the application. Of these, Claims 1-12 and 32-35 have been withdrawn from consideration as being directed to non-elected inventions. Claims 13-31 presently stand rejected under 35 U.S.C. § 102 and/or § 103. Claims 1-12, 18, 21, 22 and 24 have been canceled by the present amendment. Claims 13-17, 19, 20, 23, 25-31 remain pending in the present application. Claims 13, 20, 23, 25, 28, and 30 are amended herein. No new matter has been added by the amendments.

II. Claim Rejections under 35 U.S.C. § 102

II. A. *Wallace et al.*

Claims 20, 21, 24-28, and 31 have been rejected under 35 U.S.C. § 102(b) as being anticipated by PCT Application No. WO 93/25563 to Wallace et al., hereinafter referred to as "Wallace et al."

As per Claim 20, the Examiner argues Wallace et al. teaches a method for detecting a single nucleotide polymorphism comprising all the steps of Claim 20, including hybridizing an extension product by a hybridization tag under stringent conditions to a capture probe, the capture probe coupled to a particle that identifies the capture probe and detecting the hybridization of the extension product to the capture probe using a detectable label. The Examiner argues that the breadth of the term "particle" encompasses capture probes attached to "particles of a membrane

filter". Official Action, page 4, first paragraph. Further, the Examiner argues that the identity of the single nucleotide polymorphism is determined based on the location of hybridization by the capture probe on the filter, "which is interpreted as determining the identity of the single nucleotide polymorphism based on the identity of the particle." Official Action, page 4, paragraph 1.

Regarding Claims 21, 24-28, and 31, the Examiner argues Wallace et al. inherently teaches the use of a plurality of primers, each specific for a different single nucleotide polymorphism because Wallace et al. teaches determining which alleles are present for twenty different dimorphic, genetically unlinked loci. The Examiner also argues Wallace et al. teaches a method wherein the 3' end of the primer is immediately adjacent to the location of the single nucleotide polymorphism of interest, as recited in Claim 24. The Examiner further argues Wallace et al. teaches a single base extension, as recited in Claim 25. The Examiner also argues that Wallace et al. teaches that the single base extension is achieved by using only a single type of nucleotide triphosphate, as recited in Claim 26. The Examiner further argues Wallace et al. teaches the single base extension can be achieved by using nucleoside triphosphates, including dideoxynucleoside triphosphate, as recited in Claims 27 and 28. Finally, the Examiner argues that Wallace et al. teaches methods for diagnosing diseases caused by a specific allele, as recited in Claim 31, including sickle cell anemia or thalassemia.

The positions of the Examiner as summarized above with respect to Claims 20, 21, 24-28, and 31 are respectfully traversed as described below.

"A claim is anticipated only if each and element in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Claim 20 presently recites a method for detecting a single nucleotide polymorphism comprising: providing at least one group of at least two primers in each group, wherein each primer in the group comprises a hybridization tag that identifies the primer, and each primer in the group having a 3' and specific for a different allele of a single nucleotide polymorphism of interest; combining the at least one group of primers with a sample containing single-stranded polynucleotides under stringent conditions which allow hybridization of the primers to complementary sequences in the single-stranded polynucleotides; extending hybridized primers by primer extension to produce an extension product, the extension product comprising the hybridization tag and a detectable label; hybridizing the extension product by the hybridization tag under stringent conditions to a capture probe, the capture probe coupled to a microbead that identifies the capture probe; detecting by flow cytometry the hybridization of the extension product to the capture probe using the detectable label; and determining the identity of the single nucleotide polymorphism based on the identity of the microbead.

Claim 20 has been amended to more particularly recite that the capture probe is coupled to a microbead that identifies the capture probe, and that detecting the hybridization of the extension product to the capture probe using the detectable label is done by flow cytometry. Support for the amendments are found at paragraphs

[0050]-[0053] (microbead) and paragraph [0056] (flow cytometry) of the specification. Coupling the capture probe to a microbead which specifically identifies the capture probe and then detecting the hybridization of the extension product to the capture probe by flow cytometry provides the user multiplex capabilities, adaptability, ease of use, and cost effectiveness, thus permitting practical analysis of multiple single nucleotide polymorphisms simultaneously.

Wallace et al. does not teach or suggest a capture probe coupled to a microbead identifying the capture probe. Wallace et al. further does not teach or suggest detecting by flow cytometry the hybridization of the extension product to the capture probe using the detectable label, as set forth in amended Claim 20. Rather, Wallace et al. teaches attaching a probe to a specific location on a membrane filter, wherein the specificity of the probe is identified by virtue of the location of the probe on the filter. The number of probes that can be attached to any single filter limits the methods taught by Wallace et al. Therefore, since Wallace et al. does not teach each and every element of Claim 20, Applicants respectfully submit that maintaining a rejection under 35 U.S.C. § 102(b) based on Wallace et al. is improper. Withdrawal of the rejection of Claim 20 under 35 U.S.C. § 102(b) as being anticipated by Wallace et al., is therefore respectfully requested. Allowance of Claim 20 is also respectfully requested.

With regard to the Examiner's rejection of Claims 21, 24-28, and 31, Applicants contend that Wallace et al. do not teach or suggest all the elements of these claims, as discussed above. Since Claims 21, 24-28, and 31 depend either

directly or indirectly from Claim 20, and Wallace et al. does not teach or suggest all the elements of Claim 20 for the reasons stated above, Wallace et al. therefore does not teach or suggest all the elements of these dependent claims either. Accordingly, Applicants respectively request withdrawal of the rejections of Claims 21, 24-28, and 31 on the basis of Wallace et al. Allowance of these claims is also respectfully requested.

II. B. *Chen et al.*

Claims 20, 21, and 24-28 have been rejected under 35 U.S.C. § 102(a) as being anticipated by a journal article to Chen et al. (Genome Research, April 2000, 10:549-557), hereinafter referred to as "Chen et al.".

As per Claim 20, the Examiner argues that Chen et al. teaches a method for detecting a single nucleotide polymorphism comprising every step recited in Claim 20.

The Examiner also argues that Chen et al. inherently teaches a method including the use of a plurality of primers each specific for a different single nucleotide polymorphism because, as the Examiner asserts, Chen et al. teaches using the method taught therein for the determination of which alleles are present at four different single nucleotide polymorphisms. The Examiner further argues that Chen et al. teaches a method wherein the 3' end of said primer is immediately adjacent to the location of the single nucleotide polymorphism of interest, as recited in Claim 24. The Examiner also argues that Chen et al. teaches a single based

primer extension, as recited in Claim 25, and further that the single based extension is achieved by using only a single type of nucleotide triphosphate, as recited in Claim 26. Further, the Examiner argues that Chen et al. teaches the primer extension can be accomplished using chain terminating nucleotides, including dideoxynucleoside triphosphates, as recited in Claims 27 and 28.

The positions of the Examiner as summarized above with respect to Claims 20, 21, and 24-28 are respectfully traversed as described below.

"A claim is anticipated only if each and element in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). As previously stated, Claim 20 presently recites a method for detecting a single nucleotide polymorphism. Claim 20 presently recites in part that a group of primers is provided wherein each primer in the group comprises a hybridization tag that identifies the primer and each primer in the group has a 3' end that is specific for a different allele of a single nucleotide polymorphism of interest. Support for the amendment can be found at paragraph 0066 of the specification and in Claim 22.

Chen et al. does not teach or suggest a method for detecting a single nucleotide polymorphism comprising providing at least one group of least two primers in each group, wherein each primer in the group comprises a hybridization tag that identifies the primer and further each primer in the group has a 3' end that is specific for a different allele of a single nucleotide polymorphism of interest. In contrast, Chen et al. teaches a single capture probe used to identify both alleles of a single

nucleotide polymorphism of interest. Chen et al. teaches that for each single nucleotide polymorphism of interest, one capture oligonucleotide probe with a unique 5' sequence (referred to therein as a "ZipCode") was designed and used to assay both alleles by placing a sample of the DNA fragment in two separate wells with a different label ddNTP in each well. The labeled ddNTP is chosen based on the expected allele variance present in the single nucleotide polymorphism of interest. See Chen et al. at Figure 1 legend, page 550, column 1, and page 556, column 2 at "SBCE Reactions". Therefore, the method taught by Chen et al. does not utilize primers specific for each different allele of a single nucleotide polymorphism of interest, but rather only specific for the single nucleotide polymorphism generally, including all alleles.

Since Chen et al. does not teach each and every element of Claim 20, Applicants respectfully submit that Claim 20 is not anticipated by Chen et al. Therefore withdrawal of the rejection of Claim 20 under 35 U.S.C. § 102 as being anticipated by Chen et al., is respectfully requested. Allowance of Claim 20 is also respectfully requested.

With regard to the Examiner's rejection of Claims 21, and 24-28, Applicants contend that Chen et al. does not teach or suggest all the elements of these claims. Since Claims 21, and 24-28 depend either directly or indirectly from Claim 20 and Chen et al. does not teach or suggest all the elements of Claim 20 for the reasons stated above, Chen et al. does not teach or suggest all the elements of these dependent claims either. Applicants therefore respectfully request withdrawal of the

rejections of Claims 21, and 24-28 on the basis of Chen et al. Allowance of these claims is respectfully requested.

II. C. *Lai et al.*

Claims 13-17, and 20-23 stand rejected by the Examiner under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent Application Publication No. US2003/0049620-A1 to Lai et al. claiming priority to US Provisional Patent Application No. 60/200,635, hereinafter referred to as "Lai et al.".

As per Claim 13, the Examiner argues that Lai et al. teaches a method for detecting a single nucleotide polymorphism comprising all the steps of original Claim 13.

The Examiner also argues that Lai et al. further teaches a reverse primer comprising a detectable label, as recited in Claim 14. The Examiner also argues that Lai et al. further teaches the reverse primer is a universal primer that is universal to both alleles being tested, as recited in Claim 15. The Examiner further argues that Lai et al. teaches repeating the extension step in subsequent rounds of PCR, as recited in Claim 16. Finally, the Examiner argues that Lai et al. teaches the assay can be multiplexed, comprising a plurality of primer pairs specific for plurality of single nucleotide polymorphisms, as recited in Claim 17.

The positions of the Examiner as summarized above with respect to Claims 13-17 are respectfully traversed as described below.

"A claim is anticipated only if each and element in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Amended Claim 13 recites a method for detecting a single nucleotide polymorphism comprising providing at least one primer pair, the primer pair containing a reverse primer and a forward primer comprising a 3' end specific for an allele of a single nucleotide polymorphism of interest and a hybridization tag that identifies the primer, the hybridization tag not being complementary to the sequence containing the single nucleotide polymorphism of interest; combining the at least one primer pair with a sample containing single-stranded polynucleotides under stringent conditions which allow hybridization of the primers to complementary sequences in the single-stranded polynucleotides; extending hybridized primers by primer extension to produce an extension product wherein the extension product comprises the hybridization tag and a detectable label; hybridizing the extension products by the hybridization tag or the complement thereof under stringent conditions to a capture probe wherein the capture probe is coupled to a microbead, the microbead identifying the capture probe; detecting by flow cytometry the hybridization of the extension product to the capture probe by the presence of the detectable label; and determining the identity of the single nucleotide polymorphism based on the identity of the microbead.

Claim 13 has been amended to recite that the capture probe is coupled to a microbead, which identifies the capture probe, and detecting the hybridization of the

extension product to the capture probe by the presence of the detectable label is accomplished using flow cytometry. Support for the amendments are found at paragraphs [0050]-[0053] (microbead) and paragraph [0056] (flow cytometry) of the specification and Claim 18 (flow cytometry). Coupling the capture probe to a microbead which specifically identifies the capture probe and then detecting the hybridization of the extension product to the capture probe by flow cytometry provides the user multiplex capabilities, adaptability, ease of use, and cost effectiveness, thus permitting practical analysis of multiple single nucleotide polymorphisms simultaneously. Lai et al. does not teach or suggest detecting by flow cytometry of the capture probe coupled to the microbead the hybridization of the extension product to the captured probe by the presence of the detectable label, as set forth in amended Claim 13. Instead, Lai et al. teaches immobilizing on a planar surface different microbead populations so that they are regularly spaced in a chosen geometry. "For example, beads can be immobilized by micromachining wells in which beads can be entrapped into the surface, or by patterned activation of polymers on the surface using light activation to cross-link single beads at particular locations." Lai et al. at page 11, paragraph [0115].

As Lai et al. teaches the beads are affixed to the substrate at a particular point and in a particular pattern, Lai et al. cannot further teach or suggest that the hybridization of the extension product to the capture probe can be detected by a flow cytometry. Instead, Lai et al. teaches detecting the hybridization of the extension product to the capture probe in the specificity of the microbead by several stationary

techniques such as a scanning system coupled to a microscope objective, confocal scanning or optical tweezers. See Lai et al. at pages 15-16, paragraphs [0160]-[0177]. Therefore, the methods taught by Lai et al. do not teach or suggest detecting the hybridization of the extension product to the capture probe by flow cytometry, as presently recited in Claim 13.

Since Lai et al. does not teach each and every element of Claim 13, Applicants respectfully submit that maintaining a rejection under 35 U.S.C. § 102(e) based on Lai et al. is improper. Withdrawal of the rejection of Claim 13 under 35 U.S.C. § 102(e) as being anticipated by Lai et al. is therefore respectfully requested. Allowance of Claim 13 is also respectfully requested.

With regard to the Examiner's rejection of Claims 14-17, Applicants contend that Lai et al. does not teach or suggest all the elements of these claims. Since Claims 14-17 depend either directly or indirectly from Claim 13 and Lai et al. does not teach or suggest all the elements of Claim 13 for the reasons stated above, Lai et al. does not teach or suggest all the elements of these dependent claims either. Applicants therefore respectfully request withdrawal of the rejections of Claims 14-17 on the basis of Lai et al. Allowance of these claims is also respectfully requested.

As per Claim 20, the Examiner argues that Lai et al. teaches a method for detecting a single nucleotide polymorphism comprising all the steps of original Claim 20.

The Examiner also argues that the assay taught by Lai et al. can be multiplex, and therefore would comprise a plurality of primer pairs each specific for a different

single nucleotide polymorphism, as recited in Claim 21. The Examiner further argues that Lai et al. teaches a method wherein the at least one primer comprises a group of at least 2 primers, each primer specific for a different allele of a single nucleotide polymorphism, as recited in Claim 22. Finally, the Examiner argues that Lai et al. teaches a method comprising a plurality of primer groups, wherein each primer group is specific for a different single nucleotide polymorphism of interest, as recited in Claim 23.

The positions of the Examiner as summarized above with respect to Claims 20-23 are respectfully traversed as described below.

"A claim is anticipated only if each and element in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Claim 20, as discussed above, presently recites a method for detecting a single nucleotide polymorphism. The method comprises steps including detecting by flow cytometry the hybridization of the extension product to the capture probe using the detectable label.

Lai et al. does not teach or suggest detecting by flow cytometry of the capture probe coupled to the microbead the hybridization of the extension product to the captured probe by the presence of the detectable label, as set forth in amended Claim 20. Instead, Lai et al. teaches immobilizing on a planar surface different microbead populations so that they are regularly spaced in a chosen geometry. "For example, beads can be immobilized by micromachining wells in which beads can be

entrapped into the surface, or by patterned activation of polymers on the surface using light activation to cross-link single beads at particular locations." Lai et al. at page 11, paragraph [0115].

As Lai et al. teaches the beads are affixed to the substrate at a particular point and in a particular pattern, Lai et al. cannot further teach or suggest that the hybridization of the extension product to the capture probe can be detected by a flow cytometry. Instead, Lai et al. teaches detecting the hybridization of the extension product to the capture probe in the specificity of the microbead by several stationary techniques such as a scanning system coupled to a microscope objective, confocal scanning or optical tweezers. See Lai et al. at pages 15-16, paragraphs [0160]-[0177]. Therefore, the methods taught by Lai et al. do not teach or suggest detecting the hybridization of the extension product to the capture probe by flow cytometry, as recited in amended Claim 20.

Since Lai et al. does not teach each and every element of Claim 20, Applicants respectfully submit that maintaining a rejection under 35 U.S.C. § 102 of Claim 20 based on Lai et al. is improper. Withdrawal of the rejection of Claim 20 under 35 U.S.C. § 102 as being anticipated by Lai et al., is therefore respectfully requested. Allowance of Claim 20 is also respectfully requested.

With regard to the Examiner's rejection of Claims 21-23, Applicants note that Claims 21 and 22 have been canceled and therefore this rejection has been rendered moot. Regarding Claim 23, Applicants contend that Lai et al. does not teach or suggest all the elements of this claim. Since Claim 23 depends directly from

Claim 20 and Lai et al. does not teach or suggest all the elements of Claim 20 for the reasons stated above, Lai et al. does not teach or suggest all the elements of this dependent claim either. Applicants respectfully request withdrawal of the rejection of Claim 23 on the basis of Lai et al. Allowance of these claims is also respectfully requested.

II. D. *Huang et al.*

Claims 20-23 stand rejected by the Examiner under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,287,778 to Huang et al., hereinafter referred to as "Huang et al.".

As per Claim 20, the Examiner argues that Huang et al. teaches a method for detecting a single nucleotide polymorphism comprising all the steps as set forth in original Claim 20. The Examiner also argues that Huang et al. teaches a method further comprising a plurality of primers specific for a plurality of single nucleotide polymorphisms, as set forth in Claim 21. The Examiner further argues that Huang et al. teaches a method wherein at least one primer comprises a group of at least two primers, each primer specific for a different allele of a single nucleotide polymorphism of interest, as recited in Claim 22. Finally, the Examiner argues that Huang et al. teaches a method further comprising a plurality of primer groups, each primer group specific for a different single nucleotide polymorphism of interest, as recited in Claim 23.

The positions of the Examiner as summarized above with respect to Claims 20-23 are respectfully traversed as described below.

"A claim is anticipated only if each and element in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Claim 20 presently recites a method for detecting a single nucleotide polymorphism comprising a number of steps including detecting by flow cytometry the hybridization of an extension product to a capture probe using a detectable label.

Claim 20 presently recites that the capture probe is coupled to a microbead that identifies the capture probe, and detecting the hybridization of the extension product to the capture probe using the detectable label is done by flow cytometry. Coupling the capture probe to a microbead of the extension product to the capture probe by flow cytometry provides the user multiplex capabilities, adaptability, ease of use, and costs effectiveness, thus permitting practical analysis of multiple single nucleotide polymorphisms simultaneously.

Huang et al. does not teach or suggest detecting by flow cytometry the hybridization of the extension product to the capture probe using the detectable label, as set forth in amended Claim 20. Rather, Huang et al. teaches a labeled extension product hybridized to one or more probes which are immobilized to known locations on a solid support. See Huang et al. at column 2, lines 57-58, column 5, lines 44-46, and Figures 1 and 2. Huang et al. relies on knowing the exact location of the probe in order to identify the particular extension primer. Huang et al. does not appreciate

using uniquely identifiably microbeads in combination with flow cytometry in order to identify the single nucleotide polymorphism based on the identity of the microbead. Unlike the method recited in Claim 20, the methods taught by Huang et al. are limited to the immobilization of the probe to a known location on a solid support in order to identify a single nucleotide polymorphism of interest. Therefore, the methods taught by Huang et al. do not teach or suggest detecting the hybridization of the extension produce to the capture probe by flow cytometry as recited in Claim 20.

Since Huang et al. does not teach each and every element of Claim 20, Applicants respectfully submit that maintaining a rejection under 35 U.S.C. § 102(e) based on Huang et al. is improper. Withdrawal of the rejection of Claim 20 under 35 U.S.C. § 102(e) as being anticipated by Huang et al., is therefore respectfully requested. Allowance of Claim 20 is also respectfully requested.

With regard to the Examiner's rejection of Claims 21-23, Applicants note Claims 21 and 22 have been canceled, and therefore rejection of these claims as anticipated by Huang et al. has been rendered moot. With regard to the rejection of Claim 23, Applicants contend that Huang et al. does not teach or suggest all the elements of Claim 23. Since Claim 23 depend directly from Claim 20 and Huang et al. does not teach or suggest all the elements of Claim 20 for the reasons stated above, Huang et al. therefore does not teach or suggest all the elements of this dependent claim either. Applicants therefore respectfully request withdrawal of the rejection of Claim 23 on the basis of Huang et al. Allowance of Claim 23 is also respectfully requested.

III. Claim Rejections under 35 U.S.C. § 103

III. A. *Wallace et al. (the '611 Patent) in view of Gerry et al.*

Claims 13-17, and 19 stand rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,639,611 to Wallace et al. (hereinafter referred to as "the '611 Patent") in view of the journal article to Gerry et al. (J. Molecular Biology 292: 252-262 (1999), hereinafter referred to as "Gerry et al.").

As per Claim 13, the Examiner argues that the '611 Patent in view of Gerry et al. teach a method for detecting a single nucleotide polymorphism comprising all the steps of original Claim 13.

The Examiner also argues that the '611 Patent in view of Gerry et al. teaches the reverse primer is a universal primer that is universal to both alleles being tested, as recited in Claim 15. The Examiner further argues the combined references teach repeating the extension step in multiple rounds of PCR, as recited in Claim 16. The Examiner further argues the cited art in combination teaches a plurality of primers that are specific for a plurality of single nucleotide polymorphisms, as recited in Claim 17. Finally, the Examiner argues that since the '611 Patent teaches a method for diagnosing sickle cell anemia, this is comparable to a method for diagnosing a disease, condition, disorder or predisposition in the subject, as recited in Claim 19.

The positions of the Examiner as summarized above with respect to Claims 13-17, and 19 are respectfully traversed as described below.

To establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested by the prior art references when combined. See in re Royka 490 F.2d 981, 180 USPQ 580 (CCPA 1974). As admitted by the Examiner, the '611 Patent does not teach or suggest all the claim limitations of original Claim 13. In particular, the '611 Patent does not teach a forward primer having a hybridization tag that identifies the primer, wherein the hybridization tag is not complementary to the sequence containing the single nucleotide polymorphism of interest. Further, the '611 Patent does not teach a capture probe attached to a particle that is specific for the hybridization tag and used to hybridized to the capture probe and identify the single nucleotide polymorphism of interest.

Further regarding present Claim 13, the '616 Patent does not teach the capture probe coupled to a microbead, wherein the microbead identifies the capture probe. The '611 Patent also does not teach detecting by flow cytometry the hybridization of the extension product to the capture probe by the presence of the detectable label.

In contrast, the '611 Patent teaches analyzing the PCR reaction product by gel electrophoresis and visualization on the gel using ethidium bromide staining. Alternatively, the '611 Patent teaches analyzing the PCR product by labeling the product with biotin and capturing the product on streptravidine-agarose. The '611 Patent only teaches analyzing the products on a fixed medium and does not teach or suggest utilizing microbeads in combination with flow cytometry, which provides several advantages over a solid support medium, as discussed herein previously.

Gerry et al. does not provide for the deficiencies of the '611 Patent. Gerry et al. teaches multiplexed PCR in a single reaction using array-based detection systems. Gerry et al. focuses extensively on arrays spotted on polymer surfaces and their advantages over arrays spotted directly on glass surfaces. Gerry et al. does not teach or suggest a capture probe coupled to a microbead wherein the microbead identifies the capture probe and further detecting by flow cytometry the hybridization of the extension product to the capture probe by the presence of the detectable label.

Since all the features of Claim 13 are neither taught nor suggested by the '611 Patent and Gerry et al. either alone or in combination, it is respectfully submitted that Claim 13 is not rendered obvious by the '611 Patent in light of Gerry et al. Applicants therefore respectfully request withdrawal of the rejection of Claim 13 based on the '611 Patent in view of Gerry et al. Allowance of Claim 13 is also respectfully requested.

With regard to the Examiner's rejection of Claims 14-17, and 19, Applicants contend that the '611 Patent and Gerry et al., either alone or in combination, all the elements of these claims. Since Claims 14-17 and 19 depend either directly or indirectly from Claim 13 and the cited references do not teach or suggest all the elements of Claim 13 for the reasons stated above, the '611 Patent and Gerry et al. therefore do not teach or suggest all the elements of these dependent claims either. Applicants therefore respectfully request withdrawal of the rejection of Claims 14-17 and 19 on the basis of the '611 Patent in view of Gerry et al. Allowance of these claims is also respectfully requested.

III. B. *Lai et al. in view of Fulton et al.*

Claim 18 stands rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Lai et al. in view of the journal article to Fulton et al. (*Clinical Chemistry*, 43:9, 1749-1756 (1997), hereinafter referred to as "Fulton et al.").

The Examiner argues that Lai et al. teaches a method for detecting a single nucleotide polymorphism comprising all the steps of original Claim 18 except that the detection is by flow cytometry. The Examiner further argues that Fulton et al. teaches methods of sorting and detecting microspheres in conjunction with nucleic acids by flow cytometry and that Lai et al. teaches the capture probe is attached to a microsphere. Therefore, argues the Examiner, it would have been obvious to one of ordinary skill "to have modified the methods of Lai et al. so as to have included a flow cytometry step for the detection of hybridization of the extension product, as taught by Fulton et al." Official Action at p. 16, point 11. The Examiner states the motivation to make the combination can be found in Fulton et al., which teaches:

> that their system "represents a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular interactions..." and that their system "...is unique in its ability to provide multiplexed, high throughput analysis coupled with real-time data analysis..." offering "excellent sensitivity, precision, speed, and economy (p. 1775)." Thus, one would have been motivated to use flow cytometry to detect the microspheres taught by Lai et al. in order to take advantage of such a system as taught by Fulton et al.

Official Action at p. 16, point 11 (quoting Fulton et al.).

Applicants initially note Claim 18 has been canceled by the present amendment, and therefore the rejection of Claim 18 has been effectively rendered

moot. However, Claim 13, from which Claim 18 depended, has also been amended to include all the former elements of canceled Claim 18. As such, the Examiner's rejection of Claim 18 could be asserted to be applicable to amended Claim 13 and therefore Applicants wish to address this possibility in the present amendment. The position of the Examiner as summarized above with respect to Claim 18 and applied to amended Claim 13 is respectfully traversed as described below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation; either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim elements. MPEP 2142; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In Hodosh v. Block Drug Co., 786 F.2d 1136 (Fed. Cir. 1986), the U.S. Court of Appeals for the Federal Circuit set forth what is described as the "tenets of patent law that must be adhered to when applying §103", Id. at 1143, n.5. Those tenets set out in Hodosh are:

a) the claimed invention must be considered as a whole;

b) the references must be considered as a whole and suggest the desirability and thus obviousness of making the combination;

c) the references must be reviewed without benefit of hindsight vision afforded by the claimed invention; and

d) "ought to be tried" is not the standard with which obviousness is determined.

Applicants respectfully submit that the combination of references, upon which the rejection of the claims relies, is improper in that the suggestion or motivation to combine the references is not supported by the proposed combination of references and even if the references were combined, there is no reasonable expectation of success of a method derived from the combined teachings. At best, the cited references are simply an "invitation to experiment" and present an "obvious-to-try" situation. An "obvious-to- try" situation is held to exist

> when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued.

In re Eli Lilly & Co., 902 F.2d 943, 945, 14 U.S.P.Q.2d 1741, 1743 (Fed. Cir. 1990).

Courts have painstakingly distinguished between obviousness under 35 U.S.C. §103 and an "obvious-to-try" situation. "[W]e have consistently held that 'obvious-to-try' is not to be equated with obviousness under 35 U.S.C. §103." The Gillette Co. v. S.C. Johnson & Son, Inc., 919 F.2d 720, 725, 16 U.S.P.Q.2d 1923, 1928 (Fed. Cir. 1990).

Claim 13 presently recites a method for detecting a single nucleotide polymorphism comprising steps as described above and including hybridizing extension products by a hybridization tag or the complement thereof under stringent conditions to a capture probe wherein the capture probe is coupled to a microbead,

the microbead identifying the capture probe; detecting by flow cytometry the hybridization of the extension product to the capture probe by the presence of the detectable label; and determining the identity of the single nucleotide polymorphism based on the identity of the microbead.

Claim 13 now recites that the capture probe is coupled to a microbead, which identifies the capture probe, and detecting the hybridization of the extension product to the capture probe by the presence of the detectable label is accomplished using flow cytometry. Coupling the capture probe to a microbead which specifically identifies the capture probe and then detecting the hybridization of the extension product to the capture probe by flow cytometry provides the user multiplex capabilities, adaptability, ease of use, and cost effectiveness, thus permitting practical analysis of multiple single nucleotide polymorphisms simultaneously.

As previously stated and admitted by the Examiner, Lai et al. does not teach or suggest detecting by flow cytometry the hybridization of the extension product to the capture probe by the presence of the detectable label and determining the identity of the single nucleotide polymorphism based on the identity of the microbead, as set forth in amended Claim 13. Assuming *arguendo* that Fulton et al. teaches the step comprising detecting by flow cytometry, as recited in amended Claim 13, there is no valid motivation to combine the references because each teach different methods and one of skill in the art would have to engage in considerable experimentation in order to reconcile the two teachings. Even with considerable experimentation, there is no reasonable expectation of success if the two disparate teachings were

combined. Although the Examiner suggests Fulton et al. provides a motivation to combine the references in that Fulton et al. states the methods disclosed therein "represents a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular interactions..." (Fulton et al. at p.1775), Applicants respectfully submit that this amounts to nothing more than an invitation to one of skill in the art to further investigate. The disclosure itself does not contain a sufficient teaching of how to obtain the desired result, especially as the two references teach different methods.

Lai et al. teaches an assay wherein a label is incorporated into a DNA product and detection of such indicates a positive result. See Lai et al. (Provisional Application) at p. 2, lines 1-2 and 15-34 and Figures 4-6 and 9. In contrast, Fulton et al. teaches a competition assay in which unlabeled target DNA competes with a fluorescent probe complementary to a microsphere target. A reduction in fluorescence is indicative of a positive result. See Fulton et al. p. 1754-1755 at "DNA sequence analysis by competitive hybridization" section. Lai et al. further contrasts Fulton et al. in that it teaches treating the DNA product after PCR amplification with a single-stranded DNA nuclease to eliminate any single-stranded DNA, and particularly any labeled primer not incorporated into the DNA product "that could later compete with the hybridization capture reaction (*see* Figure 6)". Lai et al. (Provisional Application) at p. 2 lines 33-34. Thus, Lai et al. emphasizes the importance of preventing competition of non-product with product for hybridization to the microbeads.

Fulton et al. strives for the exact opposite result. As both references teach incompatible methods, there is no motivation to combine them without undue experimentation or reliance on improper hindsight reasoning. Further, there is no reasonable expectation of success by one of skill in the art even with lengthy experimentation since the methods are so fundamentally different in testing conditions and end result sought after (i.e. fluorescence increase vs. fluorescent elimination at the microbead). Fulton et al. provides at best an invitation to experiment in its boast as to broad adaptability of the method to all molecular interactions. It does not provide a suggestion as to how the incompatibilities of the two systems can be overcome, such that one of skill in the art would be motivated to try.

In summary, the cited references alone or in combination do not provide a valid motivation to combine the references to arrive at the method recited in original Claim 18 and present Claim 13, and further if the references were combined, there is no reasonable expectation of success of the combined method without further undue experimentation. The combination of references at most presents an "obvious-to-try" situation. Therefore, applicants respectfully submit that a rejection under 35 U.S.C. § 103 of Claim 13 based on Lai et al. in view of Fulton et al. would be improper. Allowance of Claim 13 over Lai et al. in view of Fulton et al. is therefore respectfully requested.

III.C. *Lai et al. in view of Wallace*

Claim 19 stands rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Lai et al. in view of Wallace et al.

As per Claim 19, the Examiner argues that Lai et al. in view of Wallace et al. teach a method for detecting a single nucleotide polymorphism comprising all the steps of original Claim 13 as applied to diagnosing a disease, condition, disorder, or predisposition, as recited in Claim 19. The Examiner admits that Lai et al. does not teach the application of the claimed method to diagnose a disease, condition, disorder, or predisposition, but argues the at the time the invention was made, it was routine to utilize the detection of single nucleotide polymorphisms for the detection of particular disease. The Examiner cites Wallace et al. as exemplary of this procedure.

The positions of the Examiner as summarized above with respect to Claim 19 are respectfully traversed as described below.

To establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested by the prior art references when combined. See in re Royka 490 F.2d 981, 180 USPQ 580 (CCPA 1974). As previously discussed, Claim 13, from which Claim 19 depends, now recites that the capture probe is coupled to a microbead identifying the capture probe and detecting the hybridization of the extension product to the capture probe by the presence of the detectable label is accomplished using flow cytometry. Coupling the capture probe to a microbead which specifically identifies the capture probe and then detecting the hybridization of the extension product to the capture probe by flow cytometry provides the user

multiplex capabilities, adaptability, ease of use, and cost effectiveness, thus permitting practical analysis of multiple single nucleotide polymorphisms simultaneously. Lai et al. does not teach or suggest detecting by flow cytometry the hybridization of the extension product to the capture probe by the presence of the detectable label, as set forth in Claim 13. In contrast, Lai et al. teaches immobilizing on a planar surface different microbead populations so that they are regularly spaced in a chosen geometry.

Wallace et al. does not provide for the deficiencies of Lai et al. As previously stated, Wallace et al. does not teach or suggest a capture probe coupled to a microbead which identifies the capture probe. Wallace et al. further does not teach or suggest detecting by flow cytometry the hybridization of the extension product to the capture probe using the detectable label, as set forth in Claim 13. Rather, Wallace et al. teaches attaching the capture probe to a specific location on a membrane filter, wherein the specificity of the probe is identified by virtue of the location of the probe on the filter.

Since all the features of Claim 19 are neither taught nor suggested by Lai et al. or Wallace et al., either alone or in combination, it is respectfully submitted that Claim 19 is not rendered obvious by Lai et al. in view of Wallace et al. Applicants therefore respectfully request withdrawal of the rejection of Claim 19 based on Lai et al. in view of Wallace et al.

III.D. *Wallace (the '611 Patent) in view of Gerry et al. and further in view of Fulton et al.*

Claim 18 stands rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over the '611 Patent in view of Gerry et al. and further in view of Fulton et al.

As per Claim 18, the Examiner argues that the '611 Patent in view of Gerry et al. teach a method for detecting a single nucleotide polymorphism comprising all the steps of original Claim 13 as set forth above. However, as admitted by the Examiner, these publications do not teach a method wherein the detection occurs utilizing flow cytometry. The Examiner further argues one of skill in the art would have been motivated to combine the teachings of Fulton et al. with those of the '611 Patent and Gerry et al. in order provide a method including all the elements of Claim 18. The Examiner finds motivation for adding the teachings of Fulton et al. in the references itself as Fulton et al. boasts the methods disclosed therein provide "a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular interactions...". Fulton et al. at p. 1775.

Applicants again note Claim 18 has been canceled by the present amendment, and therefore the rejection of Claim 18 has been effectively rendered moot. However, Claim 13 from which Claim 18 depended has also been amended to include all the former elements of canceled Claim 18. As such, the Examiner's rejection of Claim 18 could be asserted to be applicable to the present Claim 13 and therefore Applicants wish to address this possibility in the present amendment. The

position of the Examiner as summarized above with respect to Claim 18 and applied to amended Claim 13 is respectfully traversed as described below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation; either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim elements. MPEP 2142; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In Hodosh v. Block Drug Co., 786 F.2d 1136 (Fed. Cir. 1986), the U.S. Court of Appeals for the Federal Circuit set forth what is described as the "tenets of patent law that must be adhered to when applying §103", Id. at 1143, n.5. Those tenets set out in Hodosh are:

a) the claimed invention must be considered as a whole;

b) the references must be considered as a whole and suggest the desirability and thus obviousness of making the combination;

c) the references must be reviewed without benefit of hindsight vision afforded by the claimed invention; and

d) "ought to be tried" is not the standard with which obviousness is determined.

Applicants respectfully submit that the combination of references, upon which the rejection of the claims relies, is improper in that the suggestion or motivation to

combine the references is not supported by the proposed combination of references and even if the references were combined, there is no reasonable expectation of success of a method derived from the combined teachings. At best, the cited references are simply an "invitation to experiment" and present an "obvious-to-try" situation. An "obvious-to- try" situation is held to exist

> when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued.

In re Eli Lilly & Co., 902 F.2d 943, 945, 14 U.S.P.Q.2d 1741, 1743 (Fed. Cir. 1990).

Courts have painstakingly distinguished between obviousness under 35 U.S.C. §103 and an "obvious-to-try" situation. "[W]e have consistently held that 'obvious-to-try' is not to be equated with obviousness under 35 U.S.C. §103." The Gillette Co. v. S.C. Johnson & Son, Inc., 919 F.2d 720, 725, 16 U.S.P.Q.2d 1923, 1928 (Fed. Cir. 1990).

Claim 13 now recites a method for detecting a single nucleotide polymorphism comprising steps as described above and including hybridizing extension products by a hybridization tag or the complement thereof under stringent conditions to a capture probe wherein the capture probe is coupled to a microbead, the microbead identifying the capture probe; detecting by flow cytometry the hybridization of the extension product to the capture probe by the presence of the detectable label; and determining the identity of the single nucleotide polymorphism based on the identity of the microbead.

Claim 13 has been amended to recite that the capture probe is coupled to a microbead, which identifies the capture probe, and detecting the hybridization of the extension product to the capture probe by the presence of the detectable label is accomplished using flow cytometry. Coupling the capture probe to a microbead which specifically identifies the capture probe and then detecting the hybridization of the extension product to the capture probe by flow cytometry provides the user multiplex capabilities, adaptability, ease of use, and cost effectiveness, thus permitting practical analysis of multiple single nucleotide polymorphisms simultaneously.

As previously stated and admitted by the Examiner, the '611 Patent in view of Gerry et al. do not teach or suggest detecting by flow cytometry the hybridization of the extension product to the capture probe by the presence of the detectable label and determining the identity of the single nucleotide polymorphism based on the identity of the microbead, as set forth in Claim 13. Assuming *arguendo* that Fulton et al. teaches the step comprising detecting by flow cytometry as recited in Claim 13, there is no valid motivation to combine the references because each teach different methods and one of skill in the art would have to engage in considerable experimentation in order to reconcile the three teachings. Even with considerable experimentation, there is no reasonable expectation of success if the disparate teachings were combined. Although the Examiner suggests Fulton et al. provides a motivation to combine the references in that Fulton et al. states the method disclosed therein "represents a revolutionary new technology that can be applied to virtually

any application that requires analysis of molecular interactions..." (Fulton et al. at p.1775), Applicants respectfully submit that this amounts to nothing more than an invitation to one of skill in the art to further investigate. The disclosure itself does not contain a sufficient teaching of how to obtain the desired result, especially as the references teach different methods.

The '611 Patent teaches an assay wherein a label is incorporated into a DNA product and detection of such indicates a positive result. See the '611 Patent at col. 3, lines 15-25 and Figure 3. Gerry et al. teaches an assay where a label is attached to one of two primers and is only incorporated into the final DNA product by ligation if the target DNA is present. See Gerry et al. at Figure 1 and accompanying legend. In contrast, Fulton et al. teaches a competition assay in which unlabeled target DNA competes with a fluorescent probe complementary to a microsphere product. A reduction in fluorescence is indicative of a positive result. See Fulton et al. p. 1754-1755 at "DNA sequence analysis by competitive hybridization" section. Thus, both the '611 Patent and Gerry et al. emphasize incorporating label into the product and said incorporation being indicative of a positive result. Fulton et al. strives for the exact opposite result.

As these references teach incompatible methods, there is no motivation to combine without undue experimentation or reliance on improper hindsight reasoning. Further, there is no reasonable expectation of success by one of skill in the art even with lengthy experimentation since the methods are so fundamentally different in testing conditions and end result sought after (i.e. fluorescence increase vs.

fluorescent elimination at the microbead), especially when three references must be combined in order to teach all the elements recited in Claim 13. Fulton et al. provides at best an invitation to experiment in its boast as to broad adaptability of the method to all molecular interactions. It does not provide a suggestion as to how the incompatibilities of the systems can be overcome, such that one of skill in the art would be motivated to try.

In summary, the cited references alone or in combination do not provide a valid motivation to combine the references to arrive at the method recited in original Claim 18 and presently amended Claim 13, and further if the references were combined, there is no reasonable expectation of success of the combined method without further undue experimentation. The combination of references at most presents an "obvious-to-try" situation. Therefore, applicants respectfully submit that a rejection under 35 U.S.C. § 103 of Claim 13 based on the '611 Patent in view of Gerry et al. would be improper. Allowance of Claim 13 over these combination references is also respectfully requested

III. E. *Chen et al. in view of Dubiley et al.*

Claims 22-23 and 31 stand rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Chen et al. in view of the published journal article to Dubiley et al. (Nucleic Acids Research, 1999, Vol. 23, No. 18, p. e19; herinafter referred to as "Dubiley et al.").

As per Claims 22-23 and 31, the Examiner argues that Chen et al. teaches a method for detecting a single nucleotide polymorphism comprising all the steps of original Claim 20, as set forth above. However, as admitted by the Examiner, Chen et al. does not teach or suggest a method wherein said at least one primer comprises a group of at least two primers, each primer in said group having a 3' end specific for a different allele of a single nucleotide polymorphism of interest, as recited in Claim 22. The Examiner further admits Chen et al. does not teach or suggest the application of the method to the detection of disease or conditions, as recited in Claim 31. The Examiner argues one of skill in the art would have been motivated to combine the teachings of Chen et al. with those of Dubiley et al. in order provide a method including all the elements of each of Claims 22-23, and 31. The Examiner finds motivation for combining the references in Dubiley et al. because this reference teaches the use of primers that end adjacent to or overlap with the polymorphic site of interest, have comparable specificity and the use of the detection method with disease alleles would provide obvious benefits with detecting disease.

Applicants note Claim 22 has been canceled by the present amendment, and therefore the rejection of Claim 22 has been effectively rendered moot. However, Claim 20 from which Claim 22 depended has also been amended to include all the former elements of canceled Claim 20. As such, the Examiner's rejection of Claim 22 could be asserted to be applicable to Claim 20 and therefore Applicants wish to address this possibility in the present amendment. The position of the Examiner as

summarized above with respect to Claims 22-23 and 31 and applied to amended Claim 20 is respectfully traversed as described below.

As noted above, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation; either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim elements. MPEP 2142; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants respectfully submit that the combination of references, upon which the rejection of the claims relies, is improper in that the suggestion or motivation to combine the references is not supported by the proposed combination of references and further, the references discourage such a combination.

Claim 20 recites a method for detecting a single nucleotide polymorphism. Claim 20 recites in part that a group of primers is provided wherein each primer in the group comprises a hybridization tag that identifies the primer and each primer in the group has a 3' end that is specific for a different allele of a single nucleotide polymorphism of interest.

As admitted by the Examiner, Chen et al. does not teach that a group of primers is provided wherein each primer in the group comprises a hybridization tag that identifies the primer and each primer in the group has a 3' end that is specific for a different allele of a single nucleotide polymorphism of interest. Assuming arguendo

that Dubiley et al. teaches a group of primers provided wherein each primer in the group and each primer in the group has a 3' end that is specific for a different allele of a single nucleotide polymorphism of interest as recited in Claim 20, Applicants respectfully submit that there is no valid motivation to combine the references because each teach different methods and one of skill in the art would have to engage in considerable experimentation in order to reconcile the teachings.

Chen et al. teaches a rapid high-throughput readout for single-nucleotide polymorphism analysis employing capture probes linked to a "ZipCode" sequence that specifically identifies the capture probe by hybridization to a complementary sequence affixed to a microbead. The complex is then analyzed by flow cytometry. See Chen et al. at Figure 1. The entire process occurs in solution and the specificity of the microbeads permits multiplexing of numerous allele testing in one reaction tube. In contrast, Dubiley et al. teaches an assay utilizing multiprimer single nucleotide extension to identify polymorphisms at a single allele of interest. The procedure takes place on a solid substrate (biological microchips) containing gel-immobilized oligonucleotides. See Dubiley et al. at p. I, Introduction. The method of Dubiley et al. is not as amenable to large scale multiplexing as Chen et al. as the solid state techniques described by Dubiley et al. are limited by the space available on the chip. Therefore, numerous alleles cannot be screened simultaneously, as is deemed a highly desirable goal by Chen et al. See Chen et al. at Abstract and p. 549-550. In fact, Chen et al. discusses traditional technologies such as biological microchips as lacking. See Chen et al. at p. 549-550. As such, one of skill in the art

following the teachings of Chen et al. would be discouraged from incorporating other techniques relying on solid substrates as Chen et al. instructs these are inferior methods when large-scale multiplexing is desired. As such, there is no motivation to combine these references and further, Chen et al. discourages such a combination.

In summary, the cited references alone or in combination do not provide a valid motivation to combine the references to arrive at the method recited in original Claims 22-23 and 31 and presently amended Claim 20. Therefore, applicants submit that a rejection under 35 U.S.C. § 103 of amended Claim 22 and Claims 23 and 31 based on Chen et al. in view of Dubley et al. would be improper and respectfully request withdrawal of the rejections of Claim 23 and 31 based on these references.

III.F. *Chen et al. in view of Söderlund et al.*

Claims 29 and 30 stand rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Chen et al. in view of U.S. Patent No. 6,013,431 to Söderlund et al., hereinafter referred to as "Söderlund et al."

As per Claims 29 and 30, the Examiner argues that Chen et al. teaches a method for detecting a single nucleotide polymorphism comprising all the steps of original Claim 20 as set forth above. However, as admitted by the Examiner, Chen et al. does not teach or suggest a method wherein a plurality of chain-terminating nucleoside triphosphates, each comprising a unique label are used, as recited in Claims 29 and 30. The Examiner argues Söderlund et al. teaches this element and one of skill in the art would have been motivated to combine the teachings of Chen et

al. with those of Söderlund et al. in order provide a method including all the elements of each of Claims 29 and 30.

The positions of the Examiner as summarized above with respect to Claims 29 and 30 are respectfully traversed as described below.

To establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested by the prior art references when combined. See in re Royka 490 F.2d 981, 180 USPQ 580 (CCPA 1974). As previously stated, Claim 20 recites a method for detecting a single nucleotide polymorphism. Claim 20 recites in part that a group of primers is provided wherein each primer in the group comprises a hybridization tag that identifies the primer and each primer in the group has a 3' end that is specific for a different allele of a single nucleotide polymorphism of interest.

Chen et al. does not teach or suggest a method for detecting a single nucleotide polymorphism comprising providing at least one group of least 2 primers in each group, wherein each primer in the group comprises a hybridization tag that identifies the primer and further each primer in the group has a 3' end that is specific for a different allele of a single nucleotide polymorphism of interest. In contrast, Chen et al. teaches a single capture probe used to identify both alleles of a single nucleotide polymorphism of interest. Chen et al. teaches that for each single nucleotide polymorphism of interest, one capture oligonucleotide probe with a unique 5' sequence (refer to therein as a "ZipCode") was designed and used to assay both alleles by placing a sample of the DNA fragment in 2 separate wells with a different label ddNTP in each well. The label ddNTP is chosen based on the expected allele

variance present in the single nucleotide polymorphism of interest. See Chen et al. at Figure 1 legend, page 550, column 1, and page 556, column 2 at SBCE Reactions. Therefore, the method taught by Chen et al. does not utilize primers specific for each different allele of a single nucleotide polymorphism of interest, but rather only specific for the single nucleotide polymorphism generally, including all alleles.

Söderlund et al. does not provide for the deficiencies of Chen et al. Söderlund et al. also teaches one primer for identifying all polymorphisms of an allele of interest. See Söderlund et al., at least Figure 1. Söderlund et al. does not teach or suggest utilizing primers specific for each different allele of a single nucleotide polymorphism of interest.

Since all the features of amended Claim 20 are neither taught nor suggested by Chen et al. or Söderlund et al. either alone or in combination, and since Claims 29 and 30 depend directly from Claim 20, Chen et al. and Söderlund et al. do not teach or suggest all the elements of these dependent claims either. Applicants therefore respectfully request withdrawal of the rejection of Claims 29 and 30 based on Chen et al. in view of Söderlund et al.

III.G. *Wallace et al. in view of Söderlund et al.*

Claims 29 and 30 stand rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Wallace et al. in view of Söderlund et al.

As per Claims 29 and 30, the Examiner argues that Wallace et al. teaches a method for detecting a single nucleotide polymorphism comprising all the steps of original Claim 20, from which Claims 29 and 30 depend. The Examiner further argues Wallace et al. teaches the 3' end of the primer is immediately adjacent to the location of the single nucleotide polymorphism of interest and that Wallace et al. teaches a single base extension method. However, the Examiner admits Wallace et al. does not teach a plurality of chain-terminating nucleoside triphosphates, each comprising a unique label, as recited in Claims 29 and 30. The Examiner argues Söderlund et al. teaches this element and that it would have been obvious to one of skill in the art to combine the references to teach all the elements of Claims 29 and 30.

The positions of the Examiner as summarized above with respect to Claims 29 and 30 are respectfully traversed as described below.

To establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested by the prior art references when combined. See in re Royka 490 F.2d 981, 180 USPQ 580 (CCPA 1974). As previously stated, Claim 20 recites more particularly that the capture probe is coupled to a microbead that identifies the capture probe, and that detecting the hybridization of the extension product to the capture probe using the detectable label is done by flow cytometry. Coupling the capture probe to a microbead which specifically identifies the capture probe and then detecting the hybridization of the extension product to the capture probe by flow cytometry provides the user multiplex capabilities, adaptability, ease of use, and cost

effectiveness, thus permitting practical analysis of multiple single nucleotide polymorphisms simultaneously.

As previously discussed, Wallace et al. does not teach or suggest a capture probe coupled to a microbead which identifies the capture probe. Wallace et al. further does not teach or suggest detecting by flow cytometry the hybridization of the extension product to the capture probe using the detectable label, as set forth in amended Claim 20. Rather, Wallace et al. teaches attaching the capture probe to a specific location on a membrane filter, wherein the specificity of the probe is identified by virtue of the location of the probe on the filter. The methods taught by Wallace et al. are limited by the number of probes that can be attached to any single filter. The methods taught by Wallace et al. do not teach or suggest detecting the hybridization of the extension product to the capture probe by flow cytometry, and therefore are not amenable to the high-throughput multiplexing method recited in Claim 20.

Söderlund et al. does not provide for the deficiencies of Wallace et al. Söderlund et al. does not teach or suggest detecting the hybridization of the extension product to the capture probe by flow cytometry.

Since all the features of amended Claim 20 are neither taught nor suggested by Wallace et al. or Söderlund et al. either alone or in combination, and since Claims 29 and 30 depend directly from Claim 20, Wallace et al. and Söderlund et al. do not teach or suggest all the elements of these dependent claims either. Applicants therefore respectfully request withdrawal of the rejection of Claims 29 and 30 based

on Wallace et al. in view of Söderlund et al. Allowance of these claims is also respectfully requested

Claim Objections

The Examiner has objected to Claims 13, 20, and 24 based on minor informalities and requires appropriate correction.

The Examiner has objected to Claim 13 because it recites 'comprising' in step (c) of the claim where 'comprising' would be more appropriate. Applicants have amended Claim 13 as requested.

The Examiner has objected to Claim 20 because it recites "said capture probe couple to a particle". The Examiner indicates "is coupled" would help the claim to read more clearly. Applicants have amended Claim 20 as requested.

The Examiner has objected to Claim 24 because it recites that the primer is "immediately adjacent to location" and the Examiner suggests the phrase is missing a word. Applicants have canceled Claim 24.

Applicants also note Claims 23 and 25 have been amended to correct improper dependency resulting from the cancellation of claims from which they depended. Applicants also note Claims 28 and 30 have been amended to correct a typographical error. In particular, the phrase "said chain-terminating nucleotide triphosphate" has been corrected to read "said chain-terminating nucleoside triphosphate" in both claims. Support can be found for the amendment in Claims 27 and 29, from which Claims 28 and 30 depend, respectively.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,

JENKINS, WILSON & TAYLOR, P.A.

Date: June 7, 2004 By: Arles A. Taylor, Jr.

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1392/15 AAT/JD/cht

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